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Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: A systematic review and meta-analysis

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ABSTRACT

Background: Dietary interventions are an important component of cardiovascular risk factor management although their impact on cardiovascular risk and mortality remains uncertain. We have studied influence of a vegetarian diet on cardiovascular risk and mortality.

Methods: We searched MEDLINE and EMBASE for comparative studies that evaluated clinical outcomes associated with vegetarian diet as compared to non-vegetarian controls or the general population. Relevant studies were pooled using random effects meta-analysis for risk of death, ischaemic heart disease (IHD) and cerebrovascular disease. We conducted subgroup analysis according to specific type of cohort (e.g. Seventh Day Adventist [SDA]) and gender.

Results: Eight studies met the inclusion criteria with 183,321 participants ($n = 183,321$). There was significant heterogeneity in all the meta-analyses, particularly evident with the studies of SDA. In all instances, we found that SDA studies showed greater effect size as compared to non-SDA studies: death (RR 0.68 95% CI 0.45–1.02 vs RR 1.04 95% CI 0.98–1.10), ischaemic heart disease (IHD) (RR 0.60 95% CI 0.43–0.80 vs RR 0.84 95% CI 0.74–0.96) and cerebrovascular disease (RR 0.71 95% CI 0.41–1.20 vs RR 1.05 95% CI 0.89–1.24). Sex specific analyses showed that IHD was significantly reduced in both genders but risk of death and cerebrovascular disease was only significantly reduced in men.

Conclusions: Data from observational studies indicates that there is modest cardiovascular benefit, but no clear reduction in overall mortality associated with a vegetarian diet. This evidence of benefit is driven mainly by studies in SDA, whereas the effect of vegetarian diet in other cohorts remains unproven.

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1. Introduction

Cardiovascular disease is the leading global cause of death. In 2008, 7.3 million people died of ischaemic heart disease (IHD) and 6.2 million died from stroke [1]. Diet represents an important risk factor for cardiovascular disease because it is modifiable and it impacts other cardiovascular risk factors such as hypertension [2], obesity [3] and diabetes [4].

Vegetarian diet appears to be associated with favourable effects on cardiovascular health [5]. A recent meta-analysis of seven clinical trials and 32 observational studies found that vegetarian diet was associated with 4.8 mm Hg to 6.9 mm Hg reduction in systolic blood pressure [6]. Another meta-analysis of 12 studies with 1300 participants showed a significant reduction of 1.28 mmol/L in plasma triglyceride level with a vegetarian diet [7]. In addition, the vegetarian diet seems to be protective against obesity, with evidence of a five unit decrease in BMI in vegetarians compared to non-vegetarian in a study involving Seventh Day Adventists (SDAs) [8]. Cohort studies have also shown that vegetarian diet was associated with a significant reduction in prevalence of diabetes and impaired fasting glucose [9] as well as incident diabetes [10].

Previous reviews have evaluated the risk of adverse cardiovascular events with vegetarian and non-vegetarian diets. Key et al. [11] combined the data from five prospective studies and Huang et al. [12] conducted a meta-analysis of seven studies and both found similar reduction in ischaemic heart disease mortality but not in all-cause and cerebrovascular mortality. One important issue is whether any of the positive findings might actually turn out to be specific to Seventh Day Adventists who have lifestyles that may confer cardiovascular or mortality benefit beyond that derived from the vegetarian diet alone. Previous studies have not evaluated the influence of SDA subgroups of vegetarians specifically on CV outcomes. Since these individuals

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also have important lifestyle modifications that may also impact on CV outcomes and so may potentially confound previous analysis. Since these studies the Adventist Health Study-2 with 73,000 participants has been published, thus representing a substantial new contribution to the literature [13]. The addition of this new study, as well as further published data from EPIC-Oxford [14] enables more detailed evaluation as to whether the vegetarian diet is truly beneficial across subgroups of the population.

The aim of this systematic review is to update the current understanding of the risk of vegetarian diet and the risk of adverse cardiovascular mortality. In addition, another objective of this study is to determine if the relationship between CV outcomes and diet is gender specific and whether there are differences in risk estimates among Seventh Day Adventist and non-Adventist cohorts.

2. Methods

We conducted a systematic review and meta-analysis of vegetarian diet and risk of all-cause and cardiovascular mortality.

2.1. Search strategy

We searched MEDLINE and EMBASE from inception up to March 2014 (Ovid) with no language limitations using the broad free-text and indexing search terms "vegetarian OR vegan OR plant based diet" AND "acute coronary syndrome OR myocardial infarction OR heart disease OR coronary artery disease OR stroke OR cerebrovascular disease OR cerebrovascular accident OR mortality OR death." In addition, we signed up with PubMed to receive automated electronic notifications for any new articles containing the 'vegetarian'. Bibliographies of included studies and review articles were checked for additional studies.

2.2. Study inclusion criteria

We selected randomised trials and controlled observational studies (case–control or cohort design) that evaluated the association of vegetarians and non-vegetarians and cardiovascular disease and mortality. The following criteria were used for inclusion:

1. Studies with one group of participants designated as vegetarian, non-meat eaters or other groups (priests, monks, SDA, etc.) which are non-meat eaters
2. Control group which could either be the general population, or meat eaters within the same healthcare setting/community
3. Aimed to evaluate one of the following outcomes: myocardial infarction/ischaemic heart disease (IHD)/coronary heart disease, stroke/cerebrovascular disease or all cause/IHD/cerebrovascular disease related mortality.

There were no restrictions on the type of vegetarian or any restriction on the non-vegetarian control group. In addition, there was no restriction based on language, design (prospective or retrospective), sample size or other methodologies.

2.3. Study selection and extraction

Two authors (CSK and SU) independently screened titles and abstracts of studies found on the search for potentially relevant studies. Any uncertainty about inclusion was resolved by a third review (MAM or YKL). The potentially relevant studies were downloaded and their full texts were reviewed for final inclusion. Data was extracted by two authors (CSK and SU) onto pre-specified tables that included elements on study design, participants, participant selection criteria and results (including statistical adjustment). The data extracted was then checked (in an unblinded manner) by at least one other reviewer (MAM or YKL).

2.4. Quality assessment

The quality of the studies was determined by considering the ascertainment of dietary intake, ascertainment of outcomes, lost to follow-up, use of propensity matching or adjustments and generalisability of the findings. Studies of the general population were considered to be generalisable while studies of unique cohorts such as SDA, priests or monks were not generalisable. Risk of bias overall was considered to be low, moderate or high depending on the extent to which the quality assessment criteria were fulfilled. If there were >10 studies available in the meta-analysis, with no evidence of substantial statistical heterogeneity, we aimed to generate funnel plots to assess the possibility of publication bias [15].

2.5. Data analysis

Data analysis was performed using RevMan 5.2 (Nordic Cochrane Centre). Random effects meta-analysis was performed using the inverse variance method. We chose to pool the adjusted results where available to reduce the risk of confounded results. We assumed similarity between the odds ratio and other relative measures such as relative risk, rate ratios or hazard ratios because cardiovascular events and death were rare events [16]. Statistical heterogeneity was assessed using I^2 statistic [17], with I^2 values of 30–60% representing a moderate level of heterogeneity. Pre-specified sensitivity analysis was performed by evaluating the effect of gender and cohort with and without SDA.

3. Results

3.1. Study selection

Eight studies met the inclusion criteria and one of these studies was not included in the primary analysis because it was deemed to have a high risk of bias [18]. The reason for the high risk of bias classification was because not all participants completed the dietary questionnaire and some participants had mixed diets. The results were not adjusted for confounders and there was poor generalizability and comparability because the vegetarian group was a cohort of Japanese priests whose mortality rate was judged against the general male population. The process of study selection is shown in Fig. 1.

3.2. Study characteristics

The designs and participant characteristics of included studies are shown in Table 1. There were six prospective cohort studies [13,14,19–22] and two observational cohorts where it was not clear if their design was prospective or retrospective [18,23]. The total number of participants was 183,321. These studies took place between 1955 and 2009 in countries such as the USA, United Kingdom, Germany, Netherlands and Japan. The sample size ranged from 1904 to 73,308 and three studies were of SDA cohorts [13,19,23]. The definition of vegetarian, study follow up and results of the studies are shown in Table 2.

3.3. Quality assessment of included studies

The risk of bias was deemed to be moderate in five studies and low to moderate in two studies (Supplementary Table 1). All the studies ascertained the dietary intake of participants by using questionnaires or surveys and the ascertainment of death was reliable using death certificates, ICD codes and death registers. In addition, all studies had some degree of lost to follow-up or exclusions which ranged from 35 participants (0.003%) to 23,161 (24%).

All studies that used adjusted analysis adjusted for age and sex but important confounders may not have been accounted for in some of the studies. Six studies [13,14,19–22] adjusted for potential confounders and the use of adjustment was not clear in two studies [18,23]. Two important factors are BMI and smoking status and only two studies adjusted for BMI [14,20] and five adjusted for smoking status [13,14,20–22]. Four studies [13,18,19,23] were not generalizable to the general population because they were SDA cohorts or cohorts of priests. In addition, the choice of control group is an important consideration. Two studies [18,23] did not have a control group that was non-vegetarian within the same population (Table 3). These studies used standardized mortality rate for the population studied which includes both vegetarians and non-vegetarians as the control group that may bias outcomes.

3.4. Association of vegetarian diet with mortality and vascular events

3.4.1. Death

We included seven cohorts in the pooled analysis. All three Adventist cohorts demonstrated significant associations between vegetarian diet and reduced all-cause mortality, whereas the non-Adventist studies did not show any mortality reduction in vegetarians (Fig. 2). Testing for subgroup differences suggests that the findings in the Adventist cohorts are likely to be significantly different from the other cohorts ($p = 0.05$).

3.4.2. Ischaemic heart disease or cardiac adverse events

We included seven cohorts in the pooled analysis. Two of the three Adventist cohorts demonstrated significant associations between

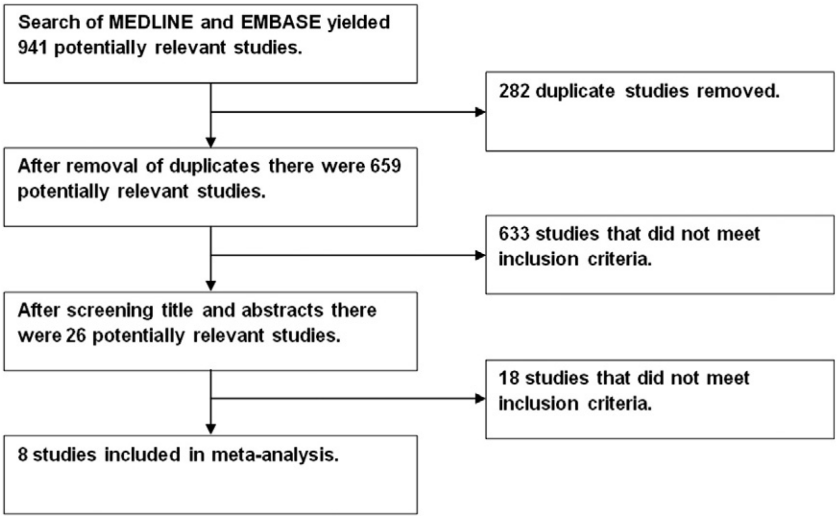

Search of MEDLINE and EMBASE yielded 941 potentially relevant studies.
282 duplicate studies removed.
After removal of duplicates there were 659 potentially relevant studies.
633 studies that did not meet inclusion criteria.
After screening title and abstracts there were 26 potentially relevant studies.
18 studies that did not meet inclusion criteria.
8 studies included in meta-analysis.

Fig. 1. Search results and study selection.

vegetarian diet and reduced cardiac adverse events, whereas the non-Adventist studies individually failed to show any benefit in vegetarians (Fig. 2). Pooled estimates for both cohorts suggest reduction in cardiac events with vegetarian diet, with a greater effect size in Adventist cohorts (RR 0.60, 95% CI 0.43–0.83) than in other datasets which showed modest benefit (RR 0.84, 95% CI 0.75–0.96) Testing for subgroup differences indicates that there is substantial heterogeneity between the pooled data in the Adventist cohorts as compared to the other cohorts ($I^2 = 71.5\%$, $p = 0.06$).

3.4.3. Cerebrovascular disease

We included six studies in the pooled analysis. One study of Adventist cohort showed significant reduction in events while the other did not and when pooled there was no significant difference (RR 0.71, 95% CI 0.41–1.20) (Fig. 2). There was no significant difference in cerebrovascular disease in any of the four non-Adventist studies and when pooled there was no significant difference (RR 1.05 95% CI 0.89–1.24). Testing for subgroup differences suggests that there is no difference between Adventist and non-Adventist cohorts ($p = 0.16$).

3.5. Vegetarian diet and gender specific risk of cardiovascular mortality

Gender specific analysis was performed with inclusion of the all male Japanese Priest Study [18] and the pooled results of Key (Table 3) [11]. From the studies in the current review, there were significant reductions in death (RR 0.82 95% CI 0.78–0.86), IHD (RR 0.81 95% CI 0.68–0.97) and cerebrovascular disease (RR 0.78 95% CI 0.68–0.89) among male but not female studies. The study by Key et al. found significant reductions in IHD for both men (RR 0.69 95% CI 0.56–0.84) and women (RR 0.80 95% CI 0.67–0.95) but no gender-specific differences

Table 1
Study design, sample size and participants.

Study	Design	Dates	Country	Sample size	Age	% male	Participants
Adventist Health Study (Beeson, 1989)	Prospective cohort study	1977 to 1982	USA	34,198	Age 25–100 years	41%	Adventist Health Study is a cohort of 34,198 non-Hispanic white Seventh-day Adventists.
Adventist Health Study 2 (Orlich, 2013)	Prospective cohort study	2002 to 2007 recruitment follow-up 2009	USA	73,308	57	34%	Adventist Health Study 2 (AHS-2) is a cohort of 96,469 Seventh-day Adventist men and women recruited at churches in the United States and Canada between 2002 and 2007.
Adventist Netherlands (Berkel, 1983)	Cohort study	1968 to 1977	Netherlands	3217	Mean age among those that died (male: 75.3 year, female: 77.4 year).	33%	Participants were Seventh-Day Adventists in Netherlands.
EPIC-Oxford study (Crowe, 2013 and Key, 2009)	Prospective cohort study	1993 to 1999	United Kingdom	44,561	44	24%	Participants were members of the UK general population.
German vegetarian study (Chang-Claude, 2005)	Prospective cohort study	1976 to 1999	Germany	1904	39.2% ≥55 years	45%	German vegetarian study included subjects who were individuals following a vegetarian or “healthy” lifestyle who were initially recruited in 1976 from readers of relevant vegetarian magazines in Germany using a short questionnaire.
Health Food Shoppers Study (Appleby, 2002 and Key, 1996)	Prospective cohort study	Recruited between 1973 and 1979	United Kingdom	10,736	Median between 45 and 46	40%	Participants were age 16–89 years at entry and had not been diagnosed with a malignant cancer before recruitment and could be classified according to their diet and smoking habits.
Japanese Zen Priest study (Ogata, 1984)	Cohort study	Jan 1955 to Dec 1978	Japan	4352	68.9% ≥50 years	100%	Participants were male Japanese Zen priests.
Oxford Vegetarian Study (Appleby, 2002 and Thorogood, 1994)	Prospective cohort study	Recruited between 1980 and 1984	United Kingdom	11,045	Median between 32 and 34	38%	Participants were age 16–89 years at entry who had not been diagnosed with a malignant cancer before recruitment and could be classified according to their diet and smoking habits.

Table 2
Definition of vegetarian, follow-up and results.

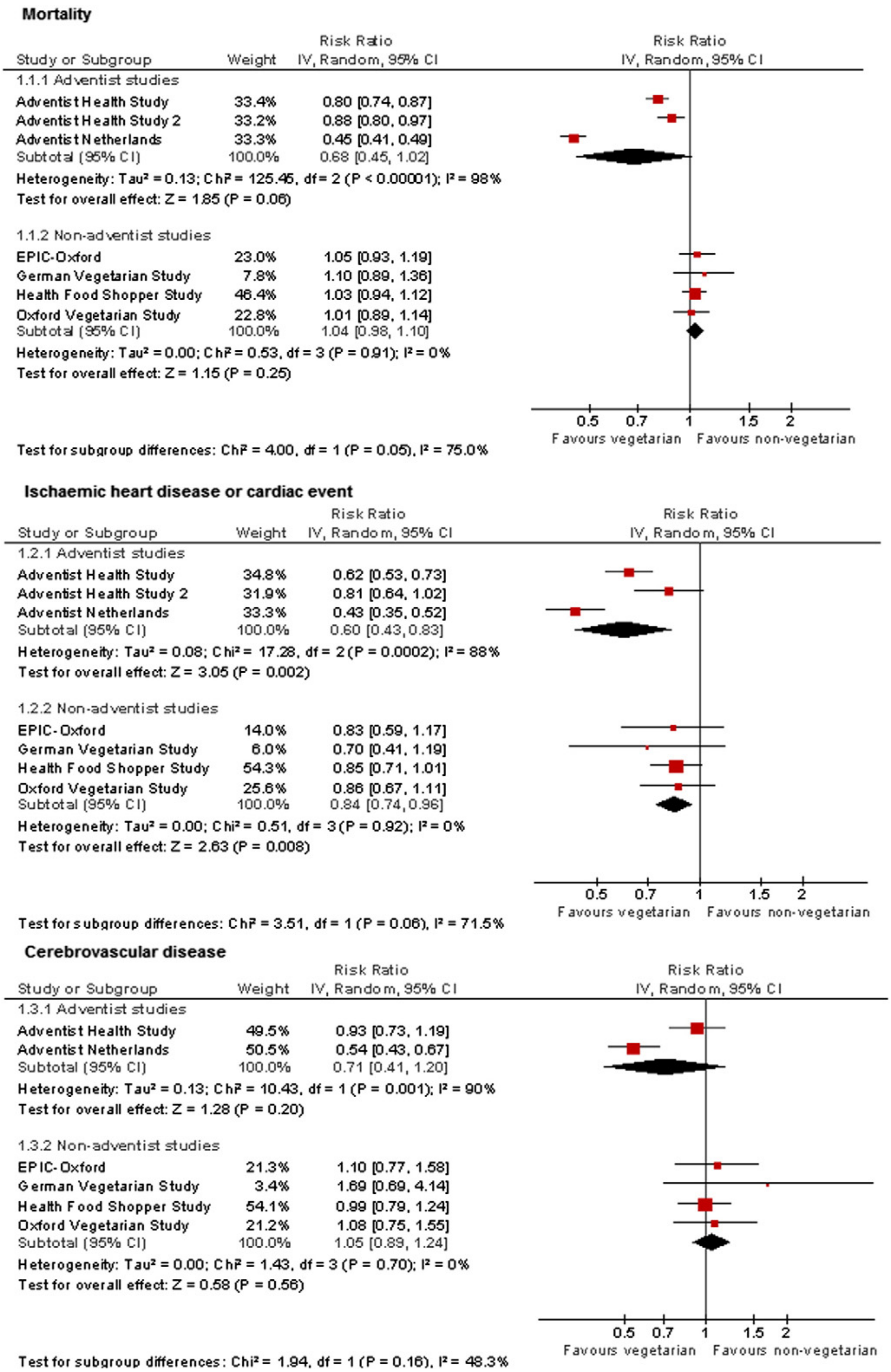
Study	Definition of vegetarian and non-vegetarian	Description of whether the vegetarian and control groups are from same cohort.	Follow-up	Outcomes
Adventist Health Study (Beeson, 1989 and Key, 1999)	Not defined.	Vegetarians and controls were from the same cohort.	6 years.	Both genders (Results from Key, 1999) n = 28,952: Total mortality: RR 0.80 (0.74–0.87) n = 3564 Ischemic heart disease: RR 0.62 (0.53–0.73) n = 921 Cerebrovascular disease: RR 0.93 (0.73–1.19) n = 319
Adventist Health Study 2 (Orlich, 2013)	Vegetarians subgrouped into vegans, lacto-ovo-vegetarians, pesco-vegetarians, semi-vegetarians. Non-vegetarians consumed non-fish meats 1 time/month or more and all meats combined more than 1 time a week.	Vegetarians and controls were from the same cohort.	5.79 years.	Both genders (Orlich, 2013): All-cause death: HR 0.88 (0.80–0.97) Ischemic heart disease death: HR 0.81 (0.64–1.02) Cardiovascular disease death: HR 0.87 (0.75–1.01) Men: All-cause death: HR 0.82 (0.72–0.94) Ischemic heart disease death: 0.71 (0.51–1.00) Cardiovascular disease death: HR 0.71 (0.57–0.90) Women: All-cause death: HR 0.93 (0.82–1.05) Ischemic heart disease death: HR 0.88 (0.65–1.20) Cardiovascular disease death: HR 0.99 (0.83–1.18)
Adventist Netherlands (Berkel, 1983)	Not defined.	Control group was the mortality rates of the Dutch population.	Study duration 9 years.	Both genders (Berkel 1983): Total mortality: standardized mortality ratio 0.45 (0.41–0.49) Ischemic heart disease: standardized mortality ratio 0.43 (0.35–0.52) Cardiovascular disease: standardized mortality ratio 0.41 (0.36–0.47) Cerebrovascular disease: standardized mortality ratio 0.54 (0.43–0.67)
EPIC-Oxford study (Crowe, 2013 and Key, 2009)	Non-vegetarians ate any meat or fish and vegetarians did not eat meat and fish.	Vegetarians and controls were from the same cohort.	11.6 years. 517,960 person-years.	Both genders: Ischemic heart disease: RR 0.83 (0.59–1.18) Both genders: Cerebrovascular disease: RR 1.10 (0.77–1.58) Both genders: Circulatory disease: RR 0.97 (0.78–1.21) Both genders: All-cause death: RR 1.05 (0.93–1.19) Men: Ischemic heart disease: HR 0.74 (0.58–0.95) Women: Ischemic heart disease: HR 0.64 (0.51–0.81)
German vegetarian study (Chang-Claude, 2005 and Chang-Claude, 1992)	Vegans, lacto-ovo vegetarian and non-vegetarian (those who occasionally or regularly eat meat and/or fish).	Vegetarians and controls were from the same cohort in 21 year follow-up study.	21 years.	Both genders 21 year follow-up (Chang-Claude, 2005): All-causes death: RR 1.10 (0.89–1.36) Ischemic heart disease death: RR 0.70 (0.41–1.18) Circulatory disease death: RR 0.83 (0.62–1.12) Key (1999): Cerebrovascular disease: RR 1.69 (0.69–4.15)
Health Food Shoppers Study (Appleby, 2002 and Key, 1996)	Vegetarians were subjects who answered yes to the question ‘Are you a vegetarian?’ but no data on either meat or fish consumption were available in this study.	Vegetarians and controls were from the same population.	18.7 years.	Both genders (Appleby, 2002): Total mortality: RR 1.03 (0.95–1.13) Ischemic heart disease: RR 0.85 (0.71–1.01) Circulatory disease: RR 0.95 (0.84–1.07) Cerebrovascular disease: RR 0.99 (0.79–1.24)
Japanese Zen Priest study (Ogata, 1984 and Huang, 2012)	Not defined.	Control group was the mortality rates of the Japanese population.	23 years.	All-cause death: RR 0.82 (0.78–0.87) Cerebrovascular disease: RR 0.78 (0.68–0.89) Heart disease: RR 0.93 (0.77–1.12)
Oxford Vegetarian Study (Appleby, 2002 and Thorogood, 1994)	Vegetarians were subjects who stated that they never ate meat or fish.	Vegetarians and controls were from the same population.	17.6 years.	Both genders (Appleby 2002): Total mortality: RR 1.01 (0.89–1.14) Ischemic heart disease: RR 0.86 (0.67–1.12) Circulatory disease: RR 0.93 (0.77–1.12) Cerebrovascular disease: RR 1.08 (0.75–1.54)

in death or cerebrovascular disease. Combining the results of the current study and those pooled in the Key study, there are significant decreases in death, IHD and cerebrovascular disease for men and only significant decreases in IHD for women.

4. Discussion

Our results suggest that vegetarian diet is potentially associated with a significant reduction in IHD. However, the purported benefit is most apparent among SDA studies whereas other studies demonstrate only a modest effect. Equally, while all of the SDA studies demonstrate significant reduction in all-cause mortality with vegetarian diet, this finding was not replicated in four of the non-Adventist studies. This raises the concern that the data supporting vegetarian diet are derived mainly from SDA studies that have different lifestyles and other factors that are not generalisable to the wider population. Heterogeneity appears to be a major issue in the overall dataset, given that we also observed gender differences where the cardiovascular and mortality risk reduction with vegetarian diet is more significant in men compared to women.

There are a number of plausible explanations (e.g. presence of unmeasured confounders, or effect of residual confounders) that can account for our findings of greater reduction in adverse cardiovascular mortality in the SDA cohorts. It is known that vegetarianism is advocated among SDA but there are additional lifestyle differences compared to the general population. The diet of SDA is characterized by a large intake of fruits, vegetables and low consumption of seafood and meat and many are lacto-ovo-vegetarians [24]. Regular SDA church



Mortality

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Adventist studies		
Adventist Health Study	33.4%	0.80 [0.74, 0.87]
Adventist Health Study 2	33.2%	0.88 [0.80, 0.97]
Adventist Netherlands	33.3%	0.45 [0.41, 0.49]
Subtotal (95% CI)	100.0%	0.68 [0.45, 1.02]
Heterogeneity: Tau² = 0.13; Chi² = 125.45, df = 2 (P < 0.00001); I² = 98%		
Test for overall effect: Z = 1.85 (P = 0.06)		
1.1.2 Non-adventist studies		
EPIC-Oxford	23.0%	1.05 [0.93, 1.19]
German Vegetarian Study	7.8%	1.10 [0.89, 1.36]
Health Food Shopper Study	46.4%	1.03 [0.94, 1.12]
Oxford Vegetarian Study	22.8%	1.01 [0.89, 1.14]
Subtotal (95% CI)	100.0%	1.04 [0.98, 1.10]
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 3 (P = 0.91); I² = 0%		
Test for overall effect: Z = 1.15 (P = 0.25)		

Test for subgroup differences: Chi² = 4.00, df = 1 (P = 0.05), I² = 75.0%

Ischaemic heart disease or cardiac event

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Adventist studies		
Adventist Health Study	34.8%	0.62 [0.53, 0.73]
Adventist Health Study 2	31.9%	0.81 [0.64, 1.02]
Adventist Netherlands	33.3%	0.43 [0.35, 0.52]
Subtotal (95% CI)	100.0%	0.60 [0.43, 0.83]
Heterogeneity: Tau² = 0.08; Chi² = 17.28, df = 2 (P = 0.0002); I² = 88%		
Test for overall effect: Z = 3.05 (P = 0.002)		
1.2.2 Non-adventist studies		
EPIC-Oxford	14.0%	0.83 [0.59, 1.17]
German Vegetarian Study	6.0%	0.70 [0.41, 1.19]
Health Food Shopper Study	54.3%	0.85 [0.71, 1.01]
Oxford Vegetarian Study	25.6%	0.86 [0.67, 1.11]
Subtotal (95% CI)	100.0%	0.84 [0.74, 0.96]
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 3 (P = 0.92); I² = 0%		
Test for overall effect: Z = 2.63 (P = 0.008)		

Test for subgroup differences: Chi² = 3.51, df = 1 (P = 0.06), I² = 71.5%

Cerebrovascular disease

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Adventist studies		
Adventist Health Study	49.5%	0.93 [0.73, 1.19]
Adventist Netherlands	50.5%	0.54 [0.43, 0.67]
Subtotal (95% CI)	100.0%	0.71 [0.41, 1.20]
Heterogeneity: Tau² = 0.13; Chi² = 10.43, df = 1 (P = 0.001); I² = 90%		
Test for overall effect: Z = 1.28 (P = 0.20)		
1.3.2 Non-adventist studies		
EPIC-Oxford	21.3%	1.10 [0.77, 1.58]
German Vegetarian Study	3.4%	1.69 [0.69, 4.14]
Health Food Shopper Study	54.1%	0.99 [0.79, 1.24]
Oxford Vegetarian Study	21.2%	1.08 [0.75, 1.55]
Subtotal (95% CI)	100.0%	1.05 [0.89, 1.24]
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 3 (P = 0.70); I² = 0%		
Test for overall effect: Z = 0.58 (P = 0.56)		

Test for subgroup differences: Chi² = 1.94, df = 1 (P = 0.16), I² = 48.3%

Fig. 2. Meta-analysis of vegetarian diet and risk of death, ischaemic heart disease and cerebrovascular disease stratified by Seventh-Day Adventist and non-Adventist cohorts.

attenders are more likely to abstain from smoking, to have good health practices and to stay married [25]. In addition, they are encouraged to avoid non-medicinal drugs, alcohol, tobacco and caffeine-containing beverages and have regular exercise, sufficient rest and maintain stable psychosocial relationships [26]. However, there is a variable degree of adherence to these practices [5].

Previous studies have highlighted dietary and non-dietary factors that might explain the lower mortality among vegetarians. The vegetarian diet is rich nutrients such as carbohydrates, n6 fatty acids, dietary fibre, carotenoids, folic acid, vitamin C, vitamin E and Mg [5]. Most vegetarian diets are low in total fat which may explain the reduction in coronary heart disease [27]. In addition, there may be harm associated with meat consumption. Several meta-analyses have shown that red meat and processed meat consumption is associated with higher all-cause mortality [28] and stroke [29], and processed meat is associated with higher CHD and diabetes [30]. Furthermore, compared to non-vegetarians, vegetarians have lower blood pressure [31], lower plasma cholesterol [11], and lower BMI [21], and the proportion of

Table 3
Summary of results.

Outcome	SDA studies Risk ratio (95% CI)	Non-SDA studies Risk ratio (95% CI)	All studies Risk ratio (95% CI)
Death	0.68 (0.45–1.02), I^2 = 98%, 3 studies[a,b,c]	1.04 (0.98–1.10), I^2 = 0%, 4 studies[d,e,f,g]	0.87 (0.68–1.11), I^2 = 97%, 7 studies[a,b,c,d,e,f,g]
Ischaemic heart disease	0.60 (0.43–0.83), I^2 = 88%, 3 studies[a,b,c]	0.84 (0.74–0.96), I^2 = 0%, 4 studies[d,e,f,g]	0.71 (0.57–0.87), I^2 = 83%, 7 studies[a,b,c,d,e,f,g]
Cerebrovascular disease	0.71 (0.41–1.20), I^2 = 90%, 2 studies[a,c]	1.05 (0.89–1.24), I^2 = 0%, 4 studies[d,e,f,g]	0.93 (0.70–1.23), I^2 = 79%, 6 studies[a,c,d,e,f,g]

Gender analysis

Outcome	Current review		Key (1999)		Combined	
	Men	Women	Men	Women	Men	Women
Death	0.82 (0.78–0.86), 2 studies[b,d]	0.93 (0.82–1.05), 1 studies[b]	0.86 (0.73–1.01), 5 studies[h]	0.93 (0.82–1.06), 5 studies[h]	0.82 (0.78–0.86), 7 studies[b,d,h]	0.93 (0.85–1.02), 6 studies[b,h]
Ischaemic heart disease	0.81 (0.68–0.97), 3 studies[b,d,e]	0.74 (0.54–1.01), 2 studies[b,e]	0.69 (0.56–0.84), 5 studies[h]	0.80 (0.67–0.95), 5 studies[h]	0.77 (0.66–0.90), 8 studies[b,d,e,h]	0.82 (0.70–0.95), 6 studies[b,e,h]
Cerebrovascular disease	0.78 (0.68–0.89), 1 studies[d]	NA	0.77 (0.57–1.02), 5 studies[h]	0.98 (0.80–1.20), 5 studiesh	0.78 (0.69–0.88), 6 studies[d,h]	0.98 (0.80–1.20), 5 studies[h]

SDA = Seventh Day Adventist.
[a] Adventist Health Study.
[b] Adventist Health Study 2.
[c] Adventist Netherlands Study.
[d] Japanese Zen Priest Study.
[e] EPIC-Oxford Study.
[f] Health Food Shopper Study.
[g] German Vegetarian Study.
[h] Adventist Mortality, Health Food Shoppers, Adventist Health, Heidelberg, Oxford Vegetarian Studies.

obese patients among vegetarians is lower than non-vegetarians [21]. In terms of non-dietary factors, the commitment to a vegetarian diet may be accompanied by health consciousness [28]. The health consciousness may also be associated higher socioeconomic class and reduced prevalence of smokers and reduced alcohol consumers [20].

While there were no specific vegetarian and non-vegetarian diet randomised trials the Ornish Lifestyle Heart Trial randomised 48 patients with moderate to severe coronary heart disease to intensive lifestyle changes which includes vegetarian diet or usual care [32]. While this study found that over 5 years there were 2.5 fewer cardiac events in the intervention group, the benefits in the intervention group may be explained by the additional requirements of 7% of caloric intake coming from fat, moderate exercise, stress management training, smoking cessation and group psychosocial support in the intervention group [33]. Furthermore, this study is significantly underpowered to draw generalisations to the general population.

Our study has some strengths and limitations. We were able to evaluate data from large datasets with long duration of follow-up which enabled the capturing of sufficient outcome events. Furthermore, we were able to stratify the analysis based on SDA and non-SDA studies as well as male and females. However, our study was limited because adherence to vegetarian diet could not be ascertained because of the nature of the data collection using dietary questionnaires and long follow-up period. In addition, the vegetarian diets may differ as one of the included studies showed different mortality rates with different types of vegetarians (vegan, lacto-ovo, pesco, semi) [13]. There were also differences in the use of adjustments for confounders and previous studies have highlighted the importance of adjusting for weight, smoking and alcohol in vegetarian studies.

Future studies should evaluate if the benefits of vegetarianism are related to diet or whether it is a marker for other health behaviours associated with vegetarianism such as decreased smoking, reduced BMI and more exercise. Furthermore, it would be useful to evaluate if there are differences between the different types of vegetarians (vegetarian, vegan, lacto-ovo, pesco, semi). In addition, studies of vegetarian diet should use statistical methods (adjustments, propensity matching, exclusion, etc.) to consider the effect of SDA members as well as the effect of obesity, smoking and alcohol. More studies are needed to understand what elements of the SDA lifestyle contribute to cardiovascular risk reduction. In addition, most of these studies have not specifically focused on patient with high cardiovascular risk, and it is unclear if adherence to a vegetarian diet may be useful as secondary prevention in patients with cardiovascular disease.

In conclusion, the reduction in IHD and all-cause mortality with vegetarian diet stems mainly from the Adventist studies, and there is much less convincing evidence from studies conducted in other populations. Once the SDA studies have been excluded, the results are either less significant or with a lesser magnitude of benefit, and this raises the concern that the non-dietary factors (confounders) in SDA lifestyle may be responsible for the risk reduction among the vegetarian studies. In addition, among men there appears to be greater benefit of vegetarian diet compared to women. In view of these inconsistent findings, we conclude that the benefits of vegetarian diet for reducing death and vascular events remain unproven.

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Conflict of interest disclosures

The authors have no conflicts of interest to declare.

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